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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/375,609	08/17/99	RHEINS L	09373/002001

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HM22/0131

EXAMINER	
PRASAD, S	
ART UNIT	**PAPER NUMBER**
1646	7

DATE MAILED: 01/31/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/375,609	Rheins et al.	
	Examiner	Art Unit	
	Sarada C Prasad	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-103* is/are pending in the application.

4a) Of the above claim(s) *11-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *64-103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

Detailed Action

1. Claims 11-63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim. Election of invention in Group I (claims 1-10) was made **without** traverse in Paper No. 6 (11/17/00). Acknowledgement is made of amendment in Paper No. 6 (11/17/00). Currently, new claims 64-103, replacing original claims 1-10, are under consideration for examination.

Specification

2. The disclosure is objected to because of the following informalities:

2a. Claim 97 does not end in a period. Each claim must begin with a capital letter and end with a period (M.P.E.P.608.0 (m)).

2b. There are two claims numbered 102, the second of the two claims has been numbered 103, according to Rule 1.126 (see M.P.E.P. Patent Rules, §1.126 Numbering of claims).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 64-103 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a non-invasive method for obtaining a skin sample for use in isolating or detecting nucleic acid encoding IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-13, IL-14 as well as factors belonging to the TGF-β superfamily, GM-CSF and IFN-γ, does not reasonably provide enablement for detecting all nucleic acids. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

3a. Instant claim 64 is overly broad in reciting "A non-invasive method for obtaining a skin sample for use in isolating or detecting nucleic acid in a skin sample,". The broad scope of the instant claim can be read to encompass that all nucleic acids in the skin sample can be detected. The specification is enabling for detection of nucleic acids encoding IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-13, IL-14 as well as factors belonging to the TGF-β superfamily, GM-CSF and IFN-γ in "skin" samples described as "a tissue comprising a sheet of cells" (page 6 of specification), and is not enabling for detecting all nucleic acids in such samples. There is no guidance provided in the specification as to how one of skill in the art would detect nucleic acid of all types other than what is exemplified in the specification. See In re Wands, 858 F.2d at 737,8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether , if experimentation is necessary, is it undue.

The independent claim 64 is broad in its scope and does not limit the list of cytokines whose levels within the "skin sample" would be useful to analyze and be reflective of events in the various layers of skin cells such as stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum and stratum basilis (dependent claims 65-69). The examples in the specification provide details on validated levels of IL-4, IL-8, IL-13, iNOS, IFN-γ during allergic contact dermatitis/irritant contact dermatitis type reactions (ACD/ICD) with GAPDH as a control in each case. However, the utility of detecting and quantitating all nucleic acids is neither supported by the disclosure nor seems to be necessary. Of course, the state of the art is such that once a correlation is established between the levels of expression of a specific cytokine in

specific skin cell types as an end point in a specific diagnosis, it is possible to detect and quantitate the levels of that cytokine. Furthermore, the expected levels of cytokines other than IL-4, IL-8, IL-13, iNOS, IFN-gamma, based on reference levels obtained in the working examples, are not necessarily identical where they have not been standardized. As a result, in the absence of guidance regarding such established indicator/prognostic value and practicality, one would have to detect all possible nucleic acids in all the layers of skin cells for determination of all endpoints.

Therefore, based on the breadth of the instant claims, the amount of guidance provided in the working examples, the level of one of skill in the art, and the level of predictability in the art it would require undue experimentation to determine all nucleic acid in the skin samples collected as claimed. Therefore, the specification is not enabled for one of skill in the art to practice the instant invention as claimed.

Claims 65-94 are rejected insofar as they depend on claim 64.

3b. Claims 66-69 recite a method of obtaining skin cell samples containing essentially stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum and stratum basilis cells. The specification is enabled to collect skin cells by the two different non-invasive methods namely tape stripping by use of adhesive or scraping the skin with an instrument to remove skin cells sample resulting in skin cells of the type described as stratum corneum cells throughout the specification. In page 6, 4th paragraph, description of the nature of these different types of skin cells is provided, however, no guidance has been provided as to how one of skill in the art would separate/distinguish these different cell types prior to isolation of the nucleic acids and quantitation of the cytokine transcripts as a reflection of a local or a systemic biological skin

reaction. The state of the art is such that histologically these different types of skin cells have been identified and distinguished, however, available methods are not sufficiently enabling for isolation of these different cell types for analytical purposes. It is possible that the Applicant may be attempting to provide enablement of the separation of these skin cell types subsequent to the filing of the application. However, the requirement of enablement of the claimed invention needs tom be fulfilled for the application in the specification as originally filed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Therefore, it would require undue experimentation for one of skill in the art to practice the invention as claimed based on the level of state of the art technology, the amount of guidance provided in the specification, and working examples.

Therefore, claims 66-69 are rejected.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 82 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 82 is indefinite in that it recites acronyms such as IL-4 (interleukin-4), IL-8 (interleukin-8), IL-13 (interleukin-13), iNOS (inducible form of nitric oxide synthase), IFN-γ (interferon γ). Use of acronyms results in indefinite language because the acronyms used to

define proteins can be subject to change or referencing more than one protein. Therefore, when used for the first time scientific terms should be completely spelled out.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 64,65,70-82, 85-91, 95-101 are rejected under 35 U.S.C. 102(b) as being anticipated by Nickoloff and Naidu (1994).

Nickoloff and Naidu (1994) disclose application of tape stripped human skin cells for determination of nucleic acid (mRNA) levels of various cytokines including TNF-α, IL-8, IL-10, IFN-γ, TGF-α, TGF- β in epidermal keratinocytes as an indicator of cytokine cascade in human epidermis. The cited reference discloses a method of collecting skin cells by stripping (page 536, Biopsy procedure, lines 1-end), thus anticipating claims 64,65,70-74. The cited reference also discloses a method of quantitating transcript levels of various cytokines by PCR using appropriate primers followed by PCR product analysis (page 536-538, reverse transcriptase-polymerase reaction analysis, lines 1-end), thus anticipating claims 76-82, 85-91, 93, 96-101.

Punch Biopsy

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 64-65,70-74, 76-82, 85-91, 93, 96-101, 103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Molen et al. (1997) in view of Kondo et al. (1994).

Kondo et al. (1994) teach a method of detection of cytokine gene expression in the epidermis during Allergic contact dermatitis (ACD) and Irritant contact dermatitis (ICD) and also compare differences during sensitization phase and elicitation phases. Kondo et al. (1994) examined a wide range of epidermal cytokines (IL-1β, IL-6 and IL-10) during cutaneous inflammatory responses, employing skin samples for nucleic acid extraction and subsequent quantitation (page 368-369, see Materials and Methods). However, the skin samples that Kondo et al. (1994) employed were collected subsequent to sacrificing of the experimental mice. Therefore, disclosure of Kondo et al. (1994) did not teach a non-invasive method of collecting skin cells (stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum and stratum basilis cells) for cytokine analysis.

It is well known in the art to collect skin cells by tape stripping or scrapping of skin to examine the stratum corneum layer of skin cells. However, Molen et al. (1997) disclose that tape stripping of human stratum corneum yields cell layers that originate from various depths and different factors can influence the actual technique (page 289, entire abstract). Therefore, it would have been prima facie obvious to one of skill in the art, at the time the invention was made, to combine the teachings of Molen et al. (1997) and Kondo et al. (1994) to collect different layers of skin cells and quantitate cytokine transcript levels in order to establish a non-invasive method of skin cell sample collection for determination of cytokine levels. The motivation for the instant invention is provided by the art recognized reliability, sensitivity and the convenience of the ability to determine cytokine levels by various assays making the instant claims 64-65,70-74, 76-82, 85-91, 93, 96-101, 103 obvious.

Conclusion

6. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarada C Prasad whose telephone number is 703-305-1009. The examiner can normally be reached Monday – Friday from 8.00 AM to 4.30 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sarada Prasad, Ph.D.
Examiner
Art Unit 1646
January 26, 2001

Prema Mertz
PREMA MERTZ
PRIMARY EXAMINER